

Quantum-assisted biomolecular modelling

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Our understanding of the physics of biological molecules, such as proteins and DNA, is limited because the approximations we usually apply to model inert materials are not in general applicable to soft, chemically inhomogeneous systems. The configurational complexity of biomolecules means the entropic contribution to the free energy is a significant factor in their behaviour, requiring detailed dynamical calculations to fully evaluate. Computer simulations capable of taking all inter-atomic interactions into account are therefore vital. However, even with the best current supercomputing facilities, we are unable to capture enough of the most interesting aspects of their behaviour to properly understand how they work. This limits our ability to design new molecules, to treat diseases, for example. Progress in biomolecular simulation depends crucially on increasing the computing power available. Faster classical computers are in the pipeline, but these provide only incremental improvements. Quantum computing offers the possibility of performing huge numbers of calculations in parallel, when it becomes available. We discuss the current open questions in biomolecular simulation, how these might be addressed using quantum computation and speculate on the future importance of quantum-assisted biomolecular modelling.

Keywords: computational biophysics, quantum computation

1. Introduction

The chemical complexity of biological macromolecules enables them to perform extraordinary functions. Biomolecular recognition, enzyme catalysis, self-organisation, and molecular motors are central to all cellular processes, but remain poorly understood theoretically. This limits our ability to develop new drugs to inhibit or promote a particular process, or to design our own nanoscale devices with bespoke functions. If we had an equivalent theoretical understanding of biological systems as we have of semiconductors, then whole new regimes of bio-inspired engineering at the nanoscale would become possible.

Experimental methods to investigate biomolecular structure at the atomic level, such as X-ray crystallography and NMR (nuclear magnetic resonance), have revolutionised our understanding of biomolecular function. Computer simulation is also extremely important in the biomolecular sciences, because it allows a physical model of the system to be constructed, but does not require such severe approximations as phenomenological models. Computer simulations at the atomistic level have proven enormously beneficial in molecular biology; for example they are routinely used to study molecular recognition and docking (which is of importance in drug design) and are integral to NMR structure refinement for biomolecules. However, due to the computational expense of the calculations, we are only able to use these methods to study small biomolecules (usually nm) for short timescales (usually ns). This

is a serious limitation; many of the important conformational changes associated with biomolecular function occur over far longer timescales (μs – ms), and many functional biomolecular systems are large protein complexes ($\sim 50\text{nm}$).

We are therefore looking in the first instance for improvements in the length of time we can run for of $\sim 10^3$ – 10^4 , and in the systems size of ~ 10 – 10^2 , a combined scaling of $\sim 10^5$ – 10^6 – a million times larger than current state-of-the-art. Ultimately, we would like to simulate much larger systems, up to the size of a whole cell, another million times larger, and beyond. Undoubtedly, a good deal of the scaling up has to be done by refining the models to be more efficient (e.g., Moritsugu et al. 2009). But without significantly more computing power it will be difficult to advance our understanding to the point where the models can deliver that level of improvement.

In this paper, we consider how future developments in quantum computing could enable our biomolecular simulations to reach new regimes. High performance quantum computing (HPQC) has recently been proposed in a fully scalable main-frame architecture based on topologically encoded photonic qubits (Devitt et al. 2008). To fully exploit HPQC for biomolecular simulation will require significant algorithm redesign to obtain a quantum mediated speed up over classical methods.

2. Biomolecules and their roles

Biomolecules are polymers made of discrete building blocks that impart functional specificity. It is the enormous diversity and versatility of these building blocks which enables biomolecules to perform such a remarkable range of functions. Cells contain proteins, nucleic acids (DNA and RNA), lipids, sugars and numerous other small organic molecules which participate in cell regulation. The nucleic acids DNA and RNA act as storage and messenger molecules for genetic information. Proteins can act by transferring biological information, many are catalysts of biochemical reactions, others are cellular scaffolds responsible for structural integrity in the cell, and some are molecular machines which couple chemical energy to a mechanical process. Organisation is vital in such a busy molecular environment. Lipid membranes compartmentalise cells into regions that perform specific functions. Communication with the rest of the cell is achieved by way of membrane proteins which act as switchable pores. To understand biology at the molecular level, it is necessary to relate the complex structure, the diverse chemistry and the anharmonic dynamics of biomolecules to their specific function within the cell.

(a) *Biomolecular structure and function*

Figure 1 shows a small but representative selection of the nucleic acid structures that are of biological importance. DNA carries the genetic code through the specific biological relationship between the sequence of the four DNA bases adenine (A), guanine (G), thymine (T) and cytosine (C) and the sequence of amino acids in a protein. The most common form of DNA is known as B-form DNA or canonical DNA (see figure 1 top left), although other forms, such as A form DNA (figure 1 top centre) and quadruplex (four-stranded) DNA (see figure 1 bottom centre), are also important. In eukaryotes, DNA is also associated with histone proteins which compact the genetic material into a structure known as chromatin so that it will

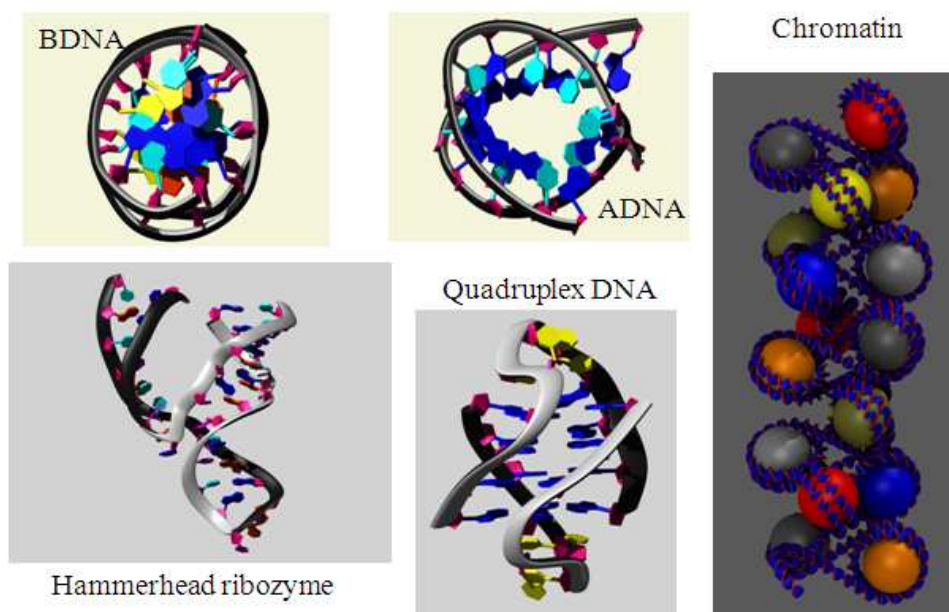


Figure 1. Nucleic acids in Nature: The most common DNA conformation is B-form DNA (top left), A-DNA (top centre) occurs under dehydrated conditions, and quadruplex DNA (bottom centre) is thought to be formed at the ends of chromosomes. Chromatin structure (right). Hammerhead ribozyme (bottom left), an RNA enzyme. Figures produced using Chimera (Pettersen et al. 2004) and VMD (Humphrey et al. 1996).

fit into the nucleus (see figure 1 right). One of the most important functional roles of RNA in the cell is to act as a messenger molecule between DNA and proteins. However, some viruses use RNA rather than DNA as their genetic material, and RNA molecules such as the Hammerhead ribozyme (see figure 1 bottom left) are also sufficiently chemically active that they can act as enzymes.

Proteins are constructed by the ribosome (shown in figure 2 bottom right), which catalyses the formation of a polymer chain made of the sequence of amino acid residues encoded by the messenger RNA template. Before the protein is biologically functional, it must fold into a tightly packed globular structure. Protein folding takes place over timescales of around $1ms$, with even the fastest folders requiring more than $10\mu s$, see Freddolino et al. (2008). In the aqueous environment of the cytoplasm, proteins often have a hydrophobic core surrounded by a hydrophilic shell whereas membrane proteins, which are located in a hydrophobic lipid environment, generally have a hydrophobic exterior and a water filled hydrophilic core. An example of a membrane protein is shown in figure 2 (top left). For a more detailed description of the biochemistry of nucleic acids and proteins, see Berg et al. (2006).

(b) *Thermodynamics of biomolecules*

Both protein folding and molecular recognition are driven by the thermodynamic requirement that the free energy is a minimum at equilibrium. Even though the cell is full of dynamical non-equilibrium processes, these take place on long

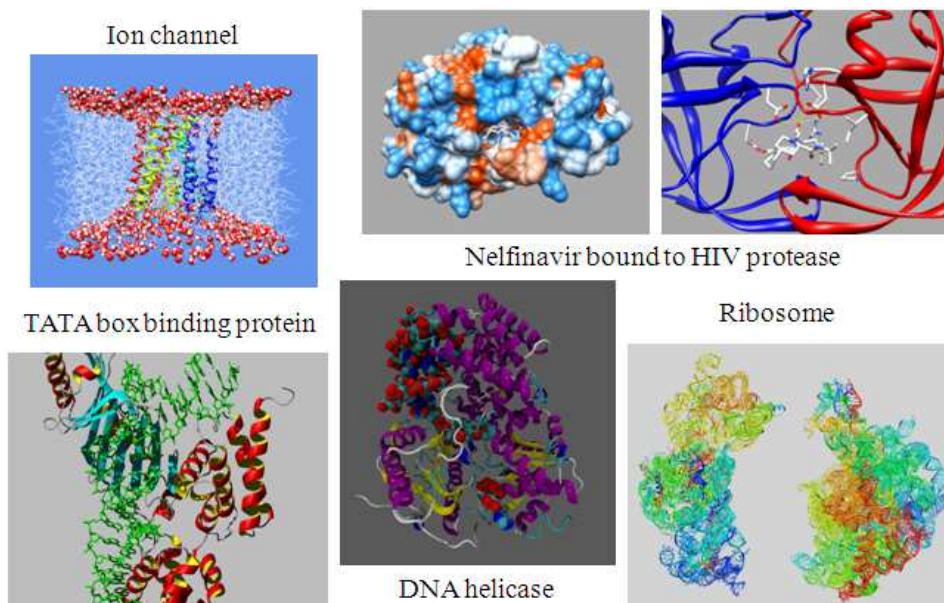


Figure 2. Protein folding, recognition and machinery. Structure of the ion channel (X) embedded in a lipid membrane (top left), two representations of the inhibitor Nelfinavir bound to HIV protease (top middle/right), TATA box binding protein bound to DNA (bottom left), DNA helicase molecular motor (bottom middle), ribosome (bottom right).

enough timescales for the biomolecules themselves to be in local thermal equilibrium. A protein adopts its native structure because folding reduces the free energy. The TATA box binding protein, shown in figure 2 (bottom left), acts as a switch to activate gene transcription. It will preferentially bind to DNA containing the sequence TATA, because this gives the most favorable change in free energy.

The changes in free energy that take place during protein folding or molecular recognition are so subtle that there is currently no theoretical method capable of either predicting the folded state of a protein from a knowledge of its amino acid sequence, or of determining the binding constant of a protein for its molecular target. The free energy change ΔG is made up of two separate contributions:

$$\Delta G = \Delta U - T\Delta S. \quad (2.1)$$

The energetic contribution ΔU is made up firstly of all of the favorable chemical interactions which promote the formation of a folded protein or a biomolecular complex. These are electrostatic interactions between oppositely charge amino acids residues, or protein/nucleic acid interactions; favorable van der Waals interactions and hydrogen bonds. In molecular recognition, these interactions occur due to shape and chemical complementarity of the reactants in a highly specific manner, in much the same way as a key fits a particular lock. An example is the interaction between the HIV protease inhibitor Nelfinavir and its molecular target, as shown in figure 2 (top centre/right). However, biomolecules are also inherently soft, and often binding an external molecule induces a conformational change that places the biomolecule under structural tension, thereby incurring an energetic penalty. This can be clearly

seen in the interaction between the TATA box binding protein and DNA (figure 2, bottom left), which forces the DNA to adopt a highly kinked structure.

As biomolecules are flexible and change shape significantly due to thermal fluctuations, the entropic term $T\Delta S$ is also important in the free energy change ΔG . In general, protein folding leads to a reduction in entropy as the unravelled polypeptide chain is constrained into its folded structure. Biomolecular association is often (but not always) accompanied by a reduction in entropy, because two previously independent molecules combine into a single complex, and because accommodating another molecule often inhibits the conformational flexibility of the participants. In addition, the solvent participates in mediating biochemical interactions. A number of the amino acids are hydrophobic. These hydrophobic residues are usually confined to the centre of the protein during folding, however, evolution has designed proteins which contain hydrophobic binding pockets which promote the binding of other hydrophobic molecules. The overall stability of the protein or biomacromolecular complex depends on the sum of all of these different competing terms.

Arguably, the most impressive macromolecular structures that have evolved act as molecular motors. Two examples of molecular machines are shown figure 2. DNA helicase (bottom centre), which separates two strands of DNA, is one of the simplest molecular machines. The ribosome (bottom right) is far larger due to its more complex function of translating the amino acid code into protein. Biological motors convert chemical energy into mechanical work (or visa versa) by amplifying localised changes in chemistry into large changes in global conformation.

3. Computer modelling of Biomolecules

The most common technique for obtaining dynamical information at the atomistic level for biomolecules is molecular dynamics (MD) simulation. MD provides the positions and velocities of all of the atoms in the system as a function of time through a numerical integration of Newton's equations using a very short time step dt (generally $2fs$). This is necessary to ensure stability of the numerical approximation and to capture the high frequency vibrations of individual bonds. The pair-wise forces acting on each atom are calculated from the gradient of an appropriate potential energy function which is known as the force-field. This force-field uses a harmonic potential to describe covalent bonds, electrostatic interactions are calculated using Coulomb's law based on a set of empirical partial charges assigned to every atom, and dispersion is modelled using the van der Waals potential. The accuracy of an MD simulation depends critically on an appropriate choice of the force-field parameters used in this potential energy function. These empirical parameters are derived from quantum mechanical calculations on molecular fragments, and are continuously under revision as the computational methods for obtaining them improve.

The environment of a biomolecule is extremely important. The most accurate MD simulations incorporate a large periodic box of water to mimic solution conditions, while simulations of membrane proteins embed the protein in lipid molecules, as shown in figure 2 (top left). The simulation of highly charged molecules, such as DNA, requires particularly careful treatment of long-range electrostatic interactions. Most biomolecular simulation codes implement the Ewald summation technique, which is achieved computationally using a Fast Fourier Transform (FFT). Despite recent advances in the efficiency and parallelisability of FFT algorithms,

this portion of the force-field calculation is still costly. For a more detailed description of modelling methods applied to biomolecules, see Leach (2001).

Given an experimentally derived structure of a drug/protein complex, atomistic simulation can provide a good estimate for the interaction energy stabilising the complex. However, as it is not computationally possible to explore the full conformational space accessible to the reactants and the products, the entropic portion of the free energy change cannot be calculated with any certainty. Hence, we are unable to accurately predict binding free energies. Pharmaceutical scientists would like to be able to predict the binding affinity of a whole combinatorial library of potential new drugs *in silico* before undertaking the expensive process of chemical synthesis, protein expression and biochemical measurements of binding free energies. Numerical studies are still widely employed in the pharmaceutical industry to test the potential of new drug molecules but the approximations employed, such as rigid molecules, mean the results are not very reliable. The study of non-equilibrium processes, such as protein folding, are even more computationally demanding, and the conformational changes associated with the action of a molecular machine such as RNA polymerase, lie way beyond our predictive abilities.

The maximum achievable simulation timescale for a (relatively small) protein containing 162 amino acids in solution ($\sim 3 \times 10^4$ total atoms) is around $10\mu\text{s}$ (Freddolino et al. 2008). Recent benchmarking studies using the AMBER molecular dynamics software indicate that it is possible to obtain around 100 ns a day on 32 CPU's for a small biomolecule, so a $10\mu\text{s}$ simulation on 32 processors requires ~ 3200 CPU days. Larger biomolecular complexes are prohibitively expensive for even nanosecond timescales: e.g. a 20 ns simulation of the ribosome, with circa 2.6 million atoms, required $\sim 10^6$ CPU hours on 768 CPUs in 2006 (Sanbonmatsu and Tung 2006), which corresponds to ~ 55 days of CPU. The ribosome synthesises new proteins at a rate of 1 amino acid every 0.1s (Wen 2008), so to capture the action of such a molecular motor would require simulation timescales $\sim 10^6$ times longer, which corresponds to 10^{12} CPU hours, or almost 1.5 million years. Using specialised hardware, MD simulations of 1ms in just over 2 months are predicted for the small protein dihydrofolate reductase ($\sim 25,000$ atoms including solvent) (Shaw, D. E., et. al 2008), faster by a factor of over 100. This speed up will allow significant progress, but a further factor of $10^3 \sim 10^4$ is needed to make real breakthroughs. The prospect of using quantum computation as a tool in molecular biology is thus very attractive, if it can deliver the necessary improvements in capabilities.

Before discussing how a quantum computer could simulate a complex system like a protein interacting with a drug, or even an entire cell, it is worth considering the nature of computer simulation and what we achieve by its use. Essentially, we are testing our most accurate models of the real world: by calculating in detail what they predict, and comparing this with our observations (for example, an experimentally determined binding constant for a protein-drug interaction). If our calculations and observations agree as well as we anticipate, this is evidence our models are appropriate and that we understand (at some level) how the system works. We may then use our computer simulations to predict things we haven't yet observed, or provide more details of processes that are hard to obtain by experiment.

That computation of any sort works in a useful way is not trivial. For some systems, we can calculate things much faster than it takes to do the experiment

(the trajectory for sending a space probe to Saturn, for example). For biomolecules, it takes far longer to run the simulation than the real system takes to do the same thing. This is because we have a simple model of Newtonian gravitation that works extremely well for satellites and planets, even though the model does not have analytic solutions for more than two bodies. While a planet is much more complex than a protein, most of this detail is irrelevant for how a space probe travels round it in orbit, so is not included in the simulations. Biomolecules are costly to simulate because far more of the details contribute to the behaviour of the system.

We do have a simple quantum-mechanical model of electrons, protons and neutrons, and how they behave when clumped together as atoms and molecules. Quantum effects are integral to chemical reactions when covalent bonds are broken and reformed, for example, during enzyme catalysis. However, in biology, most processes involve more subtle energetic changes, where quantum effects can be well-approximated using force-field parameters derived from quantum chemistry simulations, combined with classical mechanics. Notable exceptions include charge and energy transport in photosynthesis, where the key reaction takes place over a few tens of atoms (Mohseni et al. 2008; Plenio and Huelga 2008; Sarovar et al. 2009), and highly sensitive receptors for light that can distinguish polarisation (e.g., Roberts et al. 2009) or detect single photons (e.g., Lillywhite 1977). Ironically, quantum processes such as these are better understood – because of the small scales over which they take place they are accessible using today’s computers – than the largely classical processes governing the cells in which they take place.

4. Quantum computing applied to biomolecules

It is now twenty five years since Feynman (1982) and Deutsch (1985) first proposed that quantum systems should be able to process information fundamentally more efficiently than classical computers. They both (independently) perceived that a superposition of multiple quantum trajectories looks like a classical parallel computer, which calculates the result of many different input values in the time it takes for one processor to do one input value. In quantum systems, this parallel processing comes “for free” with the superposition of the quantum state, and promises an exponential saving in the memory and processing time required for suitable problems. Simulation of quantum systems was the original idea from Feynman for what a quantum computer could do better than classical, and this is expected to be one of the first useful applications of small quantum computers. For more detailed discussion, see Kendon et al. (2010). Less work has been done on how to apply quantum computers to classical simulations, where limitations in classical computing power show up just as keenly, as our discussion of biomolecular simulation makes clear. Harrow et al. (2009) provide a quantum algorithm for solving linear systems of equations, while quantum lattice gas methods (Boghosian and Taylor 1998; Meyer 2002) can be used for classical as well as quantum simulations. Solving eigenvalue equations (Abrams and Lloyd 1999) can be done exponentially more efficiently too.

In quantum chemistry it actually helps to keep a more detailed model for quantum simulations (Kassal et al. 2008), the approximations used in classical computations would slow the quantum computer down. Calculations at the quantum chemical level provide the empirical parameters essential to construct the force-fields for biomolecular simulations, one important area where quantum computers

can contribute (Fan 2009). This improves accuracy, but does not increase speed. However, it won't help us to keep the quantum details for biomolecular simulations of systems with hundreds of thousands of atoms. By using classical dynamical models we've already made an exponential saving in resources by reducing the state space from Hilbert space to classical degrees of freedom. What we need are more efficient ways to perform calculations of classical molecular dynamical systems. A quantum computer can offer a significant advantage only if we can employ a quantum algorithm with a better scaling than offered by the classical methods. Even a small polynomial (quadratic or even less) advantage would be significant in practice, given the large size of the systems we wish to simulate. There are three main ways in which a quantum computer could provide an improvement.

(a) Encode the system in a quantum superposition

This would use quantum parallelism to mimic the way current classical parallel algorithms work. A single classical computation would be carried out using exponentially less memory, at the end of which we obtain only an exponentially small amount of the full information. This is thus suitable only for problems where the result is a global average of some sort that can be efficiently extracted from the final state. It requires the whole computation to be quantum from start to finish, requiring quantum coherence to be maintained for all of a large, long computation.

(b) Perform multiple computations in superposition

The system is encoded in the same way as for classical simulations, i.e., no saving in memory, but the quantum superposition allows us to perform several computations in parallel. A single simulation could process several different initial states at the same time, or all branches of a section of the computation could be calculated simultaneously. This approach requires some sort of quantum trick to select for favored outcomes at the expense (destructive interference of) less-favored outcomes. It could be applied to protein folding; for example, here many possible configurations can be explored, but those with higher energy are penalised. Energy minimisation problems can be mapped onto adiabatic quantum computation see, for example, Perdomo et al. (2008), for discussion of how to do this with the hydrophobic-polar model for protein-folding. The potential savings here depend on how many different input states, or paths, need to be calculated to find the right one. An exponentially large superposition is possible, if required by the problem.

Multiple simultaneous computations could also be used to explore the phase space sufficiently to provide an estimate of the entropic term in the free energy. This would not increase the size of the system that can be simulated, but would provide a really important improvement in the accuracy of the calculations, since the entropic term is neglected or poorly estimated using current methods. This is thus a very attractive option for biomolecular MD simulations.

(c) Quantum subroutines

A hybrid strategy in which costly parts of the computation of a single time step are turned into more efficient quantum subroutines. This has the advantage of requiring quantum coherence only for shorter time scales, so may be feasible sooner

than fully quantum methods. There is no saving in memory, and the running time is reduced by a constant factor determined by the per time step speed up. This method is appropriate for dynamical studies where we need all the classical information.

The most obvious subroutine to quantumise, the Fourier transform, will not yield the speed up one would naively expect. Although the quantum Fourier transform (QFT) plays a key role in quantum algorithms with an exponential speed up over the best known classical, e.g., the factoring algorithm due to Shor (1997), it has been shown to be efficiently classically simulatable when either the input is a classical (separable) state, or the output is measured immediately following the QFT (Browne 2007; Aharonov et al. 2006). Both of these conditions apply here. However, a less dramatic speed up is possible, if the quantum FT processor takes less time than the classical FT, and the data can be efficiently copied between the quantum and classical processors. The FFT scales as $O(N \log N)$ while the QFT is $O(N)$, but what matters is the actual time taken, rather than the scaling, which we won't be able to determine without details of the quantum processor architecture.

This method could be applied to protein folding, or other dynamics where we have to explore a number of paths to find the optimum choice. In this case, we use a quantum subroutine to find the best move at each step, then classically implement the single chosen move. Unlike in option 2., the dynamics are obtained step by step.

5. Future perspectives

Biomolecular simulation is extremely computationally demanding, and there are no “free lunches” when it comes to processing large complex systems. Nonetheless, quantum computers have special capabilities that could make a real difference to our ability to compute and predict the properties of biological systems at the cellular level. Most importantly, it is the ability of a quantum computer to explore many classical paths simultaneously that offers a potential method to overcome the problem of finding the minimum *free energy*, as opposed to just the minimum energy, in an optimisation problem such as protein folding or molecular docking. State of the art MD simulations now routinely include “repeat” simulations, in which a number of initial conformations are investigated in parallel to check the robustness of any conclusions against thermal noise. The potentially massive parallelisation provided by a quantum computer offers the possibility of evolving a whole thermodynamic ensemble, rather than a single trajectory. Quantumised ensemble dynamics algorithms may one day make calculating the binding free energy of a complex as routine as current calculations of the binding energy. With a quantum computer, it may be as straightforward to calculate the optimal chemistry of the drug necessary to turn off a cancerous gene, for example, as it now is to calculate the precise trajectory required for a rocket to reach the moon.

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